UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/494,096	01/28/2000	Gary A. Bannon	HS 102	3034

24280 7590 08/10/2005

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/494,096
Filing Date: January 28, 2000
Appellant(s): BANNON ET AL.

Charles E Lyon
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/12/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

Claims 37-46 and 56-62 are pending and on appeal.

(4) Status of Amendments After Final

The amendment after final rejection filed on 7/12/04 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct. Example 1 corresponds to page 14 of the specification. Example 2 corresponds to page 20. Examples 3 and 4 corresponds to page 23 and 24, respectively. Examples 5 and 7 correspond to page 24 and 31 respectively.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: The rejection of claims 41 and 42 under 35 U.S.C. § 112 second paragraph is hereby withdrawn in view of amendment to the claims filed 7/12/04.

The six issues on appeal are as follows:

(1) Claims 37-46 and 56-61 lack enablement under 35 U.S.C. § 112.

(2) Claims 37-46 and 56-61 lack written description under 35 U.S.C. § 112.

(3) Claims 37 and 56-60 contain new matter under 35 U.S.C. § 112. Appellant notes that claim 37 does not include the language that the Examiner objects to under this rejection. Thus the rejection presumably only applies to claims 56-60.

(4) Claims 37-45 and 56-61 are being unpatentable under 35 U.S.C. § 103(a) over Burks et al (1997) in view of Evens et al (Therapeutic Drug Monitoring 15: 514-520, 1993).

(5) Claims 37-46 and 56-61 are being unpatentable under 35 U.S.C. § 103(a) over Stanley et al. (1997) in view of Evens et al (Therapeutic Drug Monitoring 15: 514-520, 1993).

(6) Claims 37-45 and 56-61 are unpatentable over claims 1-4 and 7 of U.S. Pat. No. 6,486,311 under the judicially created doctrine of obviousness-type double patenting.

(7) Grouping of Claims

Appellant's brief includes a statement that the enablement Rejection under 35 U.S.C. § 112 first paragraph of Claims 37-46 and 56-61 stand or fall together. The written description Rejection under 35 U.S.C. § 112 first paragraph of Claims 37-46 and 56-61 stand or fall together. The new matter rejection under 35 U.S.C. § 112 first paragraph of claim 37 stands or falls alone; The new matter rejection under 35 U.S.C. § 112 first paragraph of claims 56-60 stand or fall together. The Rejection under 35 U.S.C. § 103(a) of Claims 37-45 and 56-61 stand or fall together. The Rejection under 35 U.S.C. § 103(a) of Claims 37-46 and 56-61 stand or fall together. The obviousness-type double patenting rejection of Claims 37-45 and 56-61 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix II to the brief is correct.

(9) Prior Art of Record

6,486,311	*Burks*	*11-2002*

Ferreira *et al,* Adv Exp Med Biol 409: 127-135, 1996.

Fasler *et al,* J. Allergy and Clinical Immunology 101(4 pt 1): 521-30, April 1998.

Burks *et al,* Eur. J. Biochem. 245: 334-339, April 1997.

Stanley *et al,* Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997.

Skolnick *et al,* Trends in Biotech. 18(1): 34-39, Jan 2000.

Colman *et al,* A structural view of immune recognition by antibodies, pages 33-36, 1994.

Evens *et al,* Therapeutic Drug Monitoring 15: 514-520, 1993.

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 first enablement

Claims 37-46 and 56-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 except that at least one amino acid has been substituted in at least one

IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, (2) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, (3) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic assays and immunotherapy, **does not** reasonably provide enablement for all nucleotide molecule encoding *any* modified food allergen as set forth in claims 37-46 and 56-61 for treating any allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively. The specification discloses vector and host cell comprising said nucleotide for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific

amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

Other than the specific polynucleotide molecules encoding the specific modified peanut allergens mentioned above, there is insufficient guidance as to all nucleotides encoding all modified food allergen, much less which nucleotide corresponds to which 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid residue in at least one IgE epitope of the full length sequence from which food allergen has been modified such as substitution, deletion, or addition and whether the resulting polynucleotide encoding the modified food allergen has reduced IgE binding and increase T cell proliferation, in turn, would be useful for desensitization immunotherapy, and/or genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, all modified food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, there is insufficient working example demonstrating that all nucleotide molecule encoding any modified food allergen is effectively activate T cells for treating any allergy. Even if the nucleotide molecule is limited to modified peanut allergens, there is no in vivo working example using polynucleotide for treating peanut allergy (gene therapy). Further, there is no showing in

the specification as filed that any genetically engineered plants and animals ever made using any nucleotide molecule encoding any modified food allergen such as peanut allergens.

It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can change the function of the protein allergen. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not.

Ferreira *et al*, of record, teach nucleotide molecules for site-directed mutagenesis in a gene encoding an allergen such as the major hazel pollen allergen Cor a 1/16 which yields a modified allergen Cor a 1/16 T10 that fails to be less reactive with IgE wherein the modified hazel pollen allergen comprises at least one amino acid change such as proline to threonine (See page 128, DNA construct, Table 1, T1 P10 to T, page 132, third paragraph from bottom, in particular).

Fasler *et al*, of record, teach that peptides derived from allergen house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified allergens failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution at amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al*, of record, teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al*, of record, teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the

substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al*, of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al*, of record, teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Since there is no obvious position within the full-length polypeptide, and the corresponding polynucleotide that, when mutated, would result in loss of IgE binding, it follows that the specific nucleotides within the polynucleotide molecule that encode said polypeptide (modified allergen) would require guidance. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp, it is unpredictable which nucleotides or codon within the full length of the polynucleotide molecule of all food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp contains an IgE epitope, let alone which nucleotides and codons that after substitution, deletion, addition would encode a modified food allergen that is less reactive with IgE, or no longer binds IgE and activates T cells, in turn, would be useful for producing the modified allergen for desensitization immunotherapy. Since the nucleotide molecules encoding all modified food allergen are not enabled, it follows that the undisclosed nucleotide molecule encoding all modified food allergen wherein the modified food allergen activates T cells is not enabled. It also follows that the undisclosed nucleotide molecule in a vector for expression in a host cell is not enabled.

Even if the nucleotide molecule is limited to peanut allergen, Fasler *et al.* teach that substituting a neutral Asn residue at position 173 for a basic Lysine, or a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine, the corresponding nucleotide encoding the modified peanut allergen fails to induce T cell proliferation and cytokine production (activated T cell). Until the nucleotides or codon corresponding to the amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all food allergen have been identified and the corresponding amino acids to be substituted for said amino acid residue(s) in the at least one IgE

epitope, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the full scope of the claimed invention.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 112 written description

Claims 37-46 and 56-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all nucleotide molecules encoding *any* modified food allergen (claims 37-45), modified food allergen based on any protein obtained from a source such as legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks (claim 45), wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp (claim 46) wherein the 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid residue has been modified in any one IgE epitope as set forth in claims 56-61.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively. The specification discloses vector and host cell comprising said nucleotide for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization

immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

With the exception of the three specific polynucleotide molecules encoding the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is inadequate written description about the structure associated with function of *all* nucleotide molecule encoding *all* modified food allergen, all nucleotide molecule encoding all modified food allergen based on *any* protein obtained from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, and all nucleotide molecule encoding *any* modified food allergen based on any protein obtained from a source such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean, shrimp, much less about the nucleotides encoding all modified food allergen wherein 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid in at least one IgE epitope have been modified without the nucleotide sequence and/or the corresponding amino acid sequence. There is in adequate written description about the structure of all nucleotide molecule encoding any modified food allergen because of the following reasons: A nucleotide molecule without the nucleotide sequence, the corresponding SEQ ID NO has no structure. There are inadequate written description about which nucleotides, codon, and the corresponding amino acids in at least one IgE epitope of which protein in which food allergen to be modified or substituted, for which amino acid, in turn, the corresponding nucleotide molecule encoding the undisclosed modified food allergen has reduced IgE binding and activates T cell as compared to any unmodified food allergen for making any modified food allergen. The specification does not provide a description of structural features

that are common to IgE epitopes other than the peanut allergens specifically exemplified. The specification does not provide a description of polynucleotide encoding all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from only three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make into nucleotides encoding other modified food allergen is adequately to described the genus defined by claim 37. In fact, the specification on page 4 at lines 10-11 discloses that IgE epitopes shared no common amino acid sequence motif.

Even if the polynucleotide molecule is limited to peanut allergen, there is insufficient written description about the structure because "polynucleotide molecule" without SEQ ID NO has no structure, much less which amino acid in which IgE epitope of which protein is modified so that the modified food allergen has reduced IgE binding and activates T cells.

The specification discloses only polynucleotide molecules encoding only three peanut allergens Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of polynucleotide molecule encoding other modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 112 New Matter

Claims 37 and 56-60 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "nucleotide molecule encoding a modified food allergen wherein 1-6 amino acid residues have been modified in the at least one IgE epitope" in claim 56 represents a departure from the specification and the claims as originally filed.

Similarly, the "nucleotide molecule encoding a modified food allergen wherein 1-5 amino acid residues have been modified in the at least one IgE epitope" in claim 57 represents a departure from the specification and the claims as originally filed.

Similarly, the "nucleotide molecule encoding a modified food allergen wherein 1-4 amino acid residues have been modified in the at least one IgE epitope" in claim 58 represents a departure from the specification and the claims as originally filed.

Similarly, the "nucleotide molecule encoding a modified food allergen wherein 1-3 amino acid residues have been modified in the at least one IgE epitope" in claim 59 represents a departure from the specification and the claims as originally filed.

Similarly, the "nucleotide molecule encoding a modified food allergen wherein 1-2 amino acid residues have been modified in the at least one IgE epitope" in claim 60 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out where the supports for said phrases come from.

Claim Rejections - 35 USC § 103

The filing date of the instant claims is deemed to be the filing date of provisional applications 60/074,590 filed 2/13/98; 60/074,624 filed 2/13/1998; 60/074,633 filed 2/13/1998 and 60/073,283 filed 1/31/1998. It is noted that priority applications USSNs 08/717,933 filed September 23, 1996 and 09/141,220 filed August 27,1998 do not support the claimed limitations A *nucleotide molecule* encoding a *modified food allergen* whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen of the instant application. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

1. Claims 37-45, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (of record, Eur. J. Biochem. 245: 334-339, April 1997; PTO 892) in view of Evens *et al* (of record, Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

Burks *et al* teach modified food allergen such as Ara h1 whose amino acid sequences are substantially identical to that of an unmodified food allergen such as the ones listed in Table 1 and Fig 3 except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen Ara h1 (See entire document, Fig 1B, Fig 3, Abstract, in particular). The reference IgE epitope is being one that is recognized by a pool serum from 15 patients which is at least two individual with peanut hypersensitivity when the unmodified food allergen is contacted with serum IgE the individuals that is allergic to the unmodified food allergen (See Figure 2A, in particular). The reference modified food allergen wherein one amino acid has been modified by Ala or glycine substitution in all the IgE epitope (See Fig 3 and Figure 5, in particular). The reference IgE epitope of peanut allergen is recognized when contacted with a pool of sera such as IgE taken from a group of 10 individuals that are allergic to the unmodified food allergen such as peanut (See page 337, Figures 4-5, in particular). The reference modified amino acid is located in the center of at least one IgE epitope (See amino acids that are underline in Table 1, page 336, in particular) and the amino acid has been modified by substitution of Alanine (hydrophobic) or glycine which is neutral (See Figure 6, in particular). Claim 43 is included in this rejection because the functional property such as stimulates T cell proliferation is an inherent property of the reference modified Ara h 1 peptide fragments. Claim 45 is included in this rejection because the reference modified peanut allergen such as Ara h1 is a protein obtained from legumes. The reference modified IgE epitopes of peanut allergen has 1-6 amino acids been modified (See underline amino acid sequence of reference peptide 1 in Table 1, in particular). The reference modified IgE epitopes of peanut allergen has 1-5 amino acids been modified (See underline amino acid sequence of reference peptide 16 in Table 1, in particular). Claims 58-60 and are included in this rejection because the recitation of "1-4, 1-3, and 1-2 amino acid residues have been modified" is an obvious variation of teachings of the reference. Burks *et al* teach further teaches that the hypogenic Ara h1 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph, in particular).

The claimed invention in claims 37-43, 45, and 56-61 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen.

The claimed invention in claim 44 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen in a vector for expression in a host cell.

Evans *et al* teach that because the DNA codons (triplets) for each amino acid already are known, the DNA sequence or nucleotide molecule is then synthesized in reverse from the protein of interest (See page 515, column 2, first full paragraph, Table 1, in particular). The nucleotide encoding the protein of interest is made so that nucleotide can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleotide molecule in reverse from the modified food allergen such as peanut allergen Ara h1 as taught by Burks *et al* so that nucleotide molecule can be put into a vector such as plasmid and host cells to scale up the production of the modified allergen as taught by Evens *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Evans *et al* teach that the nucleotide encoding the protein of interest can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular). Burks *et al* teach further teaches that modified food allergen such as the hypogenic Ara h1 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph, in particular).

2. Claims 37-46, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley *et al* (of record, Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) in view of Evens *et al* (of record, Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

Stanley *et al* teach modified food allergen Ara h2 whose amino acid sequences are substantially identical to that of an unmodified food allergen Ara h2 except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen Ara h2 (See

entire document, Fig 2, Abstract, in particular). The reference IgE epitope is being one that is recognized by a pool serum from 15 patients which is at least two individual with peanut hypersensitivity when the unmodified food allergen is contacted with serum IgE the individuals that is allergic to the unmodified food allergen (See Figure 2, in particular). The reference modified food allergen wherein one amino acid has been modified such as Ala or glycine substitution in all the IgE epitope (See Table III and Figure 5, in particular). The reference IgE epitope of peanut allergen is recognized when contacted with a pool of sera such as IgE taken from a group of 15 individuals that are allergic to the unmodified food allergen such as peanut (See caption in Figure 5, in particular). The reference-modified amino acid is located in the center of at least one IgE epitope (See amino acids that are underline in reference peptide 6 and 8, Table III, in particular) and the amino acid has been modified by substitution of Alanine, which is hydrophobic, or glycine, which is neutral (See Figure 5, in particular). Claim 43 is included in this rejection because the functional property such as stimulates T cell proliferation is an inherent property of the reference modified Ara h 1 peptide fragments. Claim 45 is included in this rejection because the reference modified peanut allergen such as Ara h2 is a protein is obtained from legumes. The reference modified IgE epitopes of peanut allergen has 1-6 amino acids been modified (See underline amino acid sequence of reference peptides 6 and 8 in Table II, in particular). Claims 57-60 are included in this rejection because the recitation of "1-5, 1-4, 1-3, and 1-2 amino acid residues have been modified" is an obvious variation of teachings of the reference. Claim 46 is included in this rejection because the modified food allergen Ara h2 amino acid sequence is homologous to a protein obtained from wheat (See Table II, in particular). Stanley *et al* teach further teaches that the hypogenic Ara h2 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 252, first paragraph, in particular).

The claimed invention in claims 37-43, 45-46, and 56-61 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen.

The claimed invention in claim 44 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen in a vector for expression in a host cell.

Evans *et al* teach that because the DNA codons (triplets) for each amino acid already are known, the DNA sequence or nucleotide molecule is then synthesized in reverse from the protein of interest (See page 515, column 2, first full paragraph, Table 1, in particular). The nucleotide encoding the protein of interest is made so that nucleotide can be put into a vector such as

plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleotide molecule in reverse from the modified food allergen such as peanut allergen Ara h2 as taught by Stanley *et al* so that nucleotide molecule can be put into a vector such as plasmid and host cells to scale up the production of the modified allergen as taught by Evens *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Evans *et al* teach that the nucleotide encoding the protein of interest can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular). Stanley *et al* teach further teaches that the hypogenic Ara h2 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 252, first paragraph, in particular).

Claim Rejections - obviousness-type double patenting

Claims 37-45, and 56-61 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 7 of U.S. Patent No. 6,486,311 B1 (Nov 2002; PTO 892). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

Claim 1 of the '311 patent recites an isolated nucleotide molecule encoding the peanut allergen designated Ara h II hybridizing under standard conditions to SEQ ID NO: 1 and which encodes a protein binding to anti-Ara h II antibodies from patients with peanut allergies while claim 7 of the '311 patent recites the said nucleotide molecule wherein the peanut allergen comprises one or more mutated IgE epitopes. Therefore, claim 7 of the '311 patent includes the limitations in the instant claim 37-45, and 56-61 because a species of the nucleotide molecule encoding the modified food allergen such as peanut Ara h II as taught by the '311 patent anticipates a genus of nucleotide molecule encoding the modified food allergen of instant claims 37-45, and 56-61. Further, the method of making the modified food allergen such as Ara h1 as evidence in the instant specification on page 25, (Table 4, amino acids critical to IgE binding of

Ara h1) is the same as that of Table 6, col. 18 of the '331 patent. Likewise, the method of making the modified food allergen such as Ara h2 as evidence in the instant specification on page 26, Table 5 is the same as that of Table 10, col. 28 of '311 patent. The method of producing the modified food allergen as evidence by page 16 (peptide synthesis) is the same as that of the '311 patent (col. 11, line 51 through col. 12, in particular.

(11) Response to Argument

Claim Rejections - 35 USC § 112 enablement

At page 5 of the Brief, Appellant submits that the present application provides explicit exemplification of nucleotide molecules encoding modified peanut allergens and method of preparing them. The disputed enablement issue in this case is whether in light of the teachings of the specification, undue experimentation is required to obtain modified food allergens other than those that are specifically exemplified in the specification. Appellant begins by summarizing Wands on page 6-7. At page 8, Appellant argues that acknowledged by the Examiner, the present application provides explicit exemplification of nucleotide molecules that encode modified peanut allergens that fall within the scope of claims. The present application clearly states that its teachings are also applicable to other food allergens (e.g., see pages 7-9). The present application clearly sets forth all the steps necessary to identify and prepare suitable nucleotide molecules encoding modified food allergens that fall within the scope of claim 37, namely:

1. Identifying a food allergen whose sequence is to be modified - the sequences of numerous food allergens were known at the time of filing, a number of these are highlighted in the specification, e.g., see pages 7-9; others were known as evidenced by the numerous references and accession numbers that are provided in the official list of allergens," maintained by the HJIS Allergen Nomenclature Subcommittee and provided as **Attachment III**.

2. Identifying and modifying IgE binding sites within the food allergen –IgE binding sites were known for a number of food allergens including allergens from milk, egg, codfish, hazel nut, soybean and shrimp (see references cited on page 7); in addition, methods of identifying and modifying IgE binding sites were known and further described in the specification (e.g., see Examples 1 and 2).

3. Introducing mutations into the sequence food allergen - methods for producing recombinant allergens and for performing site-directed mutagenesis were well known and routine at the time of filing (e.g., see page 11 and Example 3).

4. Screening mutants for those with reduced IgE binding as the natural food allergen (and optionally substantially the same T-cell activity and/or IgG binding) - those skilled in the of nucleotide molecules encoding the art were familiar with the methods that were used by the inventors to allergens for IgG and IgE binding and T-cell stimulation (e.g., see page 9 and the Examples). Thus, as in Wands, at the time the application was filed, the starting materials necessary to obtain nucleotide molecules encoding modified protein allergens were available and the techniques for performing the necessary steps were well known and routine. The level of skill in the art was high.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The instant claims encompass all nucleotide molecule encoding all modified food allergen whose amino acid sequence has at least one amino acid has been modified in at least one IgE epitope by substitution, deletion, addition (claims 37, 39, 41) such as hydrophobic amino acid substitute for a neutral or hydrophilic amino acid (claim 42) wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified food allergen (claim 38), wherein at least one modified amino acid is located in the center of at least one IgE epitope (claim 40), wherein 1-6 (claim 56) , or 1-5 (claim 57), 1-4 (claim 58), 1-3 (claim 59), 1-2 (claim 60) or one amino acid residue (claim 61) have been modified at least any IgE epitope of all food allergen.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively. The specification discloses vector and host cell comprising said nucleotide for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope

wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

Other than the specific polynucleotide molecules encoding the specific modified peanut allergens mentioned above, there is insufficient guidance as to all nucleotides encoding all modified food allergen, much less which nucleotide corresponds to which 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid residue in at least one IgE epitope of the full length sequence from which food allergen has been modified such as substitution, deletion, or addition and whether the resulting polynucleotide encoding the modified food allergen has reduced IgE binding and increase T cell proliferation, in turn, would be useful for desensitization immunotherapy, and/or genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, all modified food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, there is insufficient working example demonstrating that all nucleotide molecule encoding any modified food allergen is effectively activate T cells for treating any allergy. Even if the nucleotide molecule is limited to modified peanut allergens, there is no in vivo working example using polynucleotide for treating peanut allergy (gene therapy). Further, there is no showing in the specification as filed that any genetically engineered plants and animals ever made using any nucleotide molecule encoding any modified food allergen such as peanut allergens.

It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can change the function of the protein allergen. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not.

Ferreira *et al*, of record, teach nucleotide molecules for site-directed mutagenesis in a gene encoding an allergen such as the major hazel pollen allergen Cor a 1/16 which yields a modified allergen Cor a 1/16 T10 that fails to be less reactive with IgE wherein the modified hazel pollen allergen comprises at least one amino acid change such as proline to threonine (See page 128, DNA construct, Table 1, T1 P10 to T, page 132, third paragraph from bottom, in particular).

Fasler *et al*, of record, teach that peptides derived from allergen house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified allergens failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution at amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

In contrast to appellant's argument that the specification highlights that substitutions at different position in peanut with different amino acids achieved the same results, the specification on page 23 discloses that substituting amino acids at position 144, 145, 147 and 148 of SEQ ID NO: 12 (Ara h1) for Met or Ala results in less than 1% of peanut specific IgE binding to these peptides. However, the substitution of an alanine (Ala) for Arginine at position 152 of Ara h1 shown in SEQ ID NO: 2 resulted in increased IgE binding.

Burks *et al*, of record, teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al*, of record, teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the

substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al*, of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al*, of record, teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Since there is no obvious position within the full-length polypeptide, and the corresponding polynucleotide that, when mutated, would result in loss of IgE binding, it follows that the specific nucleotides within the polynucleotide molecule that encode said polypeptide (modified allergen) would require guidance. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp, it is unpredictable which nucleotides or codon within the full length of the polynucleotide molecule of all food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp contains an IgE epitope, let alone which nucleotides and codons that after substitution, deletion, addition would encode a modified food allergen that is less reactive with IgE, or no longer binds IgE and activates T cells, in turn, would be useful for producing the modified allergen for desensitization immunotherapy. Since the nucleotide molecules encoding all modified food allergen are not enabled, it follows that the undisclosed nucleotide molecule encoding all modified food allergen wherein the modified food allergen activates T cells is not enabled. It also follows that the undisclosed nucleotide molecule in a vector for expression in a host cell is not enabled.

Even if the nucleotide molecule is limited to peanut allergen, Fasler *et al.* teach that substituting a neutral Asn residue at position 173 for a basic Lysine, or a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine, the corresponding nucleotide encoding the modified peanut allergen fails to induce T cell proliferation and cytokine production (activated T cell). Until the nucleotides or codon corresponding to the amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all food allergen have been identified and the corresponding amino acids to be substituted for said amino acid residue(s) in the at least one IgE

epitope, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the full scope of the claimed invention.

At page 9 of the Brief, appellant argues that there is no particular magic in the sequence of the peanut allergens Ara h1 2, 3 that makes these protein allergens more susceptible to the inventive methods; the inventive principles, as discussed in the present application, apply to other protein allergens as well. In fact, quite the opposite might be expected. Peanut proteins are highly allergenic and, like many other food allergens (as distinguished, for example from most pollens and danders) present a significant risk of anaphylaxis to those allergic to them. The inventive demonstration that such anaphylactic proteins can be modified so that IgE binding is reduced as compared with the unmodified protein provides a strong teaching to those of ordinary skill in the art that other modified protein allergens with reduced IgE binding can also be made.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. In contrast to appellant's assertion that other nucleotide molecule encoding modified protein allergens with reduced IgE binding can also be made without guidance, Burks *et al,* of record, teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al,* of record, teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Fasler *et al,* of record, teach that peptides derived from allergen house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with

alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular). In fact, the specification on page 23 discloses that substituting amino acids at position 144, 145, 147 and 148 of SEQ ID NO: 12 (Ara h1) for Met or Ala results in less than 1% of peanut specific IgE binding to these peptides. However, the substitution of an alanine (Ala) for Arginine at position 152 of Ara h1 shown in SEQ ID NO: 2 resulted in increased IgE binding. Thus the effects of these changes to the polypeptide of any allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable.

At pages 9-10 of the Brief, appellant argues that others have prepared modified protein allergens according to the teachings of the application without undue experimentation. Appellant cites various post filing date references, i.e. Robotham et al for teaching linear IgE epitope mapping of the English walnut (*Juglans regia*) major food allergen, Jug r1", J. Allergy Clin. Immuol. 109: 143-149, 2002. Astwood et al., "identification and characterization of IgE binding epitopes of patatin, a major food allergen of potato", J Allerp Clin. Immunol. 105:5184 (Abstract 555), 2000. Helm et al., "Mutational analysis of the IgE-binding epitopes of P34/Gly m Bd 30K", J Allergy Clin. Immunol. 105:378-384, 2000. Ayuso et al., "identification and mutational analysis of major epitopes of the shrimp allergen Pen a 1 (Tropomyosinl", J Allergy Clin. Immunol. 105:S140 (Abstract 423), 2000. and Lehrer et al., "current understanding of food allergens", Ann. .NY Acad Sci. 964:69-85, 2002 to show that the inventive principles, once demonstrated may be readily applied to other protein allergens, including food allergens.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The instant claims encompass all nucleotide molecule encoding all modified food allergen whose amino acid sequence has at least one amino acid has been modified in at least one IgE epitope by substitution, deletion, addition (claims 37, 39, 41) such as hybrophobic amino acid substitute for a neutral or hydrophilic amino acid (claim 42) wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified food allergen (claim 38), wherein at least one modified amino acid is located in the center of at least one IgE

epitope (claim 40), wherein 1-6 (claim 56) , or 1-5 (claim 57), 1-4 (claim 58), 1-3 (claim 59), 1-2 (claim 60) or one amino acid residue (claim 61) have been modified at least any IgE epitope of all food allergen. It is noted that the pending claims are not drawn to a method of making modified peanut allergen.

With respect to the Robotham et al reference, Robotham et al merely describes the mapping of a linear IgE epitope of English walnuts. Robotham et al do not teach nucleotide molecule encoding modified English walnut nor nucleotide molecule encoding any modified food allergen as required by the claims. Robotham et al teach allergen specific IgE binding epitopes could be linear or conformational (See page 147, col. 2, last paragraph, in particular). Robotham et al further teach "to date, no common structural character of liner IgE epitopes has been identified" (See page 148, col. 1, first paragraph, in particular). The identification of only one linear IgE epitope to English walnut is unique in that all previously analyzed allergens contain multiple linear IgE epitopes as well as conformational epitopes and that conformational epitopes are important and key in IgE binding (See page 148, col. 1, first paragraph, in particular). More importantly, the mutational analysis of Jug r1 IgE binding epitope as shown in Table I on page 145 of the reference shows that amino acid substitution from Q to A at position 1 increases IgE binding whereas amino acid substitution from E to A at position leads to decrease IgE binding. Again, there is no obvious position within each peptide, the corresponding polynucleotide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding. Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable.

With respect to the Astwood et al reference (J Allergy Clin Immunol January 2000), the abstract merely states that the authors have identified the major and minor IgE binding epitopes of potato allergen and have identified within these IgE epitopes the amino acid residues that when substitute would reduce or abolish IgE binding to these peptides. However, the abstract does not discloses the amino acids residues within which IgE epitopes of the full length polypeptide to be substituted, the amino acid sequence of the IgE epitope. Similarly, Astwood et al do not teach nucleotide molecule encoding modified potato allergen nor nucleotide molecule encoding any modified food allergen as required by the claims.

With respect to the Ayuso et al reference (J Allergy Clin Immunol January 2000), the abstract states that there are five major IgE binding regions of shrimp allergen Pen a1 (region 1:

43-57, region 2: 85-105, region 3: 133-153, region 4: 187-201 and region 5: 247-284). The abstract further states that amino acid substitutions in the center of the IgE epitope sequence are more likely to eliminate IgE binding by 59.5% as compared to substitutions in the peripheral parts of the epitope (39.1%), which means that approximately 40% of the chance that amino acid substitution in the center of the IgE epitope sequence has no effect or increase IgE binding, and approximately 60% the chance that substitutions in the peripheral parts of the epitope has no effect or increase IgE binding. The abstract further states that single amino acid non-conservative amino acid substitution in the center of the IgE epitope are most likely to reduce or abolish IgE antibody binding (63.5%) as compared to 23.1% conservative substitution, which means that approximately 36.5% of the chance that the non-conservative amino acid substitution has no effect or increase IgE binding. Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable. Ayuso et al do not teach nucleotide molecule encoding all modified shrimp allergen nor nucleotide molecule encoding any modified food allergen as required by the claims.

With respect to the Helm et al reference (J. Allergy Clin Immunol 105: 378-84, Feb 2000), the state of the prior art as exemplified by Helm et al is such that determining which amino acid within the IgE epitope when mutated would reduced IgE binding is empirical by nature and the effect of amino acid substitution is unpredictable. Helm et al teach that alanine substitutions in IgE epitope 6 at amino acid position 6 and 7 and epitope 16 at position 7 showed reduced IgE binding. However, IgE epitopes 1, 13 and 15 could not be mutagenized to a non-IgE-binding peptide with alanine substitution at any position in the peptide with serum from patients (See col. 2, paragraph bridging page 380 and 381, col. 1, page 381, in particular). Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable. Again, Helm et al do not teach nucleotide molecule encoding any modified food allergen as required by the claims.

With respect to the Lehrer et al reference, Lehrer et al teach that one amino acid substitution may have no effect, reduced or abolished IgE binding, or even enhanced IgE binding. This certainly has signification implications when assessing IgE antibody reactivity to food allergen epitopes. Generally, greater than two substitutions usually abolished IgE-binding ability to modified shrimp allergen Pen a 1 peptides (IgE epitopes) (See page 79, last paragraph, in particular). Lehrer et al echo the teachings of Ayuso et al that substitutions from the epitope center are more likely to eliminate (59.5% IgE binding) as opposed to substitutions on the epitope

periphery (39.1%) discussed earlier. (See paragraph bridging page 79 and 80, in particular). Lehrer et al teach "whether these observations for IgE binding epitopes of tropomyosin from shrimp are relevant to those other food allergens *is not clear*. Generally, our results are consistent with those reported of major peanut allergens Ara h1, 2, and 3[37-39]." (See page 80, paragraph 1, in particular). To paraphrase the teachings of Burks et al on the mutagenesis of IgE epitope in Ara h1, "there is no obvious position within each IgE epitope that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, Eur. J. Biochem 245: 334-339, 1997 in particular). To paraphrase the teachings of Stanley et al on the mutagenesis of IgE epitope in Ara h2, each IgE epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each IgE epitope peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding (See page 251, Arch. Biochem. Biophys. 342(2): 244-253, 1997, in particular). Thus the effects of these changes to the polypeptide of any food allergen, the corresponding polynucleotide encoding the modified allergen are largely unpredictable. Given the indefinite number of polynucleotide molecule encoding all modified food allergen, the limited amount of guidance as to which nucleotides or codon corresponding to the amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all food allergen to be modified by substitution, deletion, addition or combination thereof, the lack of sufficient working examples in the specification as filed, and the unpredictability in the art as discussed supra, it would require undue experimentation of one skilled in the art to practice the full scope of claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Until the nucleotides or codon corresponding to the amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all food allergen have been identified and the corresponding amino acids to be substituted for said amino acid residue(s) in the at least one IgE epitope, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the claimed invention.

At page 10-11 of the Brief, Appellant asserts that the Examiner's argument fail to establish a case of lack of enablement, Appellant argues the examiner has conceded that the specification enables for nucleotides molecules that encode the specific modified peanut allergens. The embodiment corresponds to the modified Ara h2 protein of Examples 3, 5 and 7.

The examiner is essentially taking the position that the specification does not enable any variations from this specifically modified Ara h2 protein. A skilled person having read the present application would be incapable of preparing without undue experimentation a nucleotide molecule encoding a modified Ara h2 with a different substitution (e.g. methionine instead of alanine) and/or a mutation at one of the other sites identified in Table 5. Appellant state that the present specification sets forth the complete amino acid of peanut Ara h2 (SEQ ID NO. 2), and also the nucleotide sequences of gene that encodes it (SEQ ID NO: 3). The specification further sets out the amino acid sequences of each of 10 IgE epitopes mapped in the Ara h 2 protein (Table 2). The specification further describes particular alanine or methionine substitutions that were introduced into the mapped IgE binding sites, and shows that some of these substitutions result in decreased IgE binding (Table 5). The specification specifically highlights that substitutions at different positions, and with different amino acids, achieved the same results.

Appellant's arguments have been fully considered but are not found to be persuasive. It is noted that the pending claims are not drawn to polynucleotide molecule encoding modified peanut allergen Ara h1, Ara h2 or Ara h3. The scope of the pending claims encompass all nucleotide molecule encoding all modified food allergen whose amino acid sequence has at least one amino acid has been modified in at least one IgE epitope by substitution, deletion, addition (claims 37, 39, 41) such as hybrophobic amino acid substitute for a neutral or hydrophilic amino acid (claim 42) wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified food allergen (claim 38), wherein at least one modified amino acid is located in the center of at least one IgE epitope (claim 40), wherein 1-6 (claim 56) , or 1-5 (claim 57), 1-4 (claim 58), 1-3 (claim 59), 1-2 (claim 60) or one amino acid residue (claim 61) have been modified at least any IgE epitope of all food allergen. The examiner's position is that a skilled person having read the present application would be incapable of preparing without undue experimentation a nucleotide molecule encoding any modified food allergen other than peanut allergen whose amino acid sequence has been modified in at least one amino acid in at least one IgE epitope as set forth in claims 37-46 and 56-61. It is agreed that other than the specific nucleotide molecule encoding the specific modified peanut allergens Ara h1, Ara h2 and Ara h3, the specification does not enable the full scope of the claimed invention. The Examiner disagrees for reasons discussed supra.

At page 12 of the Brief, Appellant argues that a claim limited to the particular substitutions that the inventors happened to have made prior to filing their patent application is

virtually useless. The examiner fails to recognize that even though the possibility exits that modification of IgE binding epitopes may not identify suitably modified protein, as was the case in Wands, practitioners would be prepared to test more than one modification and to screen for nucleotide molecules that encode useful modified proteins.

This is not found to be persuasive for the following reasons. The instant claims encompass all nucleotide molecule encoding all modified food allergen whose amino acid sequence has at least one amino acid has been modified in at least one IgE epitope by substitution, deletion, addition (claims 37, 39, 41) such as hydrophobic amino acid substitute for a neutral or hydrophilic amino acid (claim 42) wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified food allergen (claim 38), wherein at least one modified amino acid is located in the center of at least one IgE epitope (claim 40), wherein 1-6 (claim 56) , or 1-5 (claim 57), 1-4 (claim 58), 1-3 (claim 59), 1-2 (claim 60) or one amino acid residue (claim 61) have been modified at least any IgE epitope of all food allergen. The pending claims are not drawn to polynucleotide encoding modified peanut allergen Ara h1, Ara h2 and Ara h3. The examiner's position is that it would take undue experimentation for one skill in the art to practice the full scope of the claimed invention.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively. The specification discloses vector and host cell comprising said nucleotide for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would

bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

Other than the specific polynucleotide molecules encoding the specific modified peanut allergens mentioned above, there is insufficient guidance as to all nucleotides encoding all modified food allergen, much less which nucleotide corresponds to which 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid residue in at least one IgE epitope of the full length sequence from which food allergen has been modified such as substitution, deletion, or addition and whether the resulting polynucleotide encoding the modified food allergen has reduced IgE binding and increase T cell proliferation, in turn, would be useful for desensitization immunotherapy, and/or genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, all modified food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, there is insufficient working example demonstrating that all nucleotide molecule encoding any modified food allergen is effectively activate T cells for treating any allergy. Even if the nucleotide molecule is limited to modified peanut allergens, there is no in vivo working example using polynucleotide for treating peanut allergy (gene therapy). Further, there is no showing in

the specification as filed that any genetically engineered plants and animals ever made using any nucleotide molecule encoding any modified food allergen such as peanut allergens.

It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can change the function of the protein allergen. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not.

Ferreira *et al*, of record, teach nucleotide molecules for site-directed mutagenesis in a gene encoding an allergen such as the major hazel pollen allergen Cor a 1/16 which yields a modified allergen Cor a 1/16 T10 that fails to be less reactive with IgE wherein the modified hazel pollen allergen comprises at least one amino acid change such as proline to threonine (See page 128, DNA construct, Table 1, T1 P10 to T, page 132, third paragraph from bottom, in particular).

Fasler *et al*, of record, teach that peptides derived from allergen house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 for alanine or glycine. However, these modified allergens failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al*. further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution at amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al*, of record, teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al*. further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al*, of record, teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the

substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al,* of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al*, of record, teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Since there is no obvious position within the full-length polypeptide, and the corresponding polynucleotide that, when mutated, would result in loss of IgE binding, it follows that the specific nucleotides within the polynucleotide molecule that encode said polypeptide (modified allergen) would require guidance. Given the indefinite number of undisclosed nucleotide molecule encoding all modified food allergen, food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp, it is unpredictable which nucleotides or codon within the full length of the polynucleotide molecule of all food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp contains an IgE epitope, let alone which nucleotides and codons that after substitution, deletion, addition would encode a modified food allergen that is less reactive with IgE, or no longer binds IgE and activates T cells, in turn, would be useful for producing the modified allergen for desensitization immunotherapy. Since the nucleotide molecules encoding all modified food allergen are not enabled, it follows that the undisclosed nucleotide molecule encoding all modified food allergen wherein the modified food allergen activates T cells is not enabled. It also follows that the undisclosed nucleotide molecule in a vector for expression in a host cell is not enabled.

Even if the nucleotide molecule is limited to peanut allergen, Fasler *et al.* teach that substituting a neutral Asn residue at position 173 for a basic Lysine, or a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine, the corresponding nucleotide encoding the modified peanut allergen fails to induce T cell proliferation and cytokine production (activated T cell). Until the nucleotides or codon corresponding to the amino acid residue(s) in the at least one IgE epitope essential for IgE antibody binding in all food allergen have been identified and the corresponding amino acids to be substituted for said amino acid residue(s) in the at least one IgE

epitope, the specification merely extends an invitation for one skill in the art to further experimentation to arrive at the full scope of the claimed invention.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 112 written description

At paragraph bridging page 12-13 of the Brief, Appellant submits that there is a strong presumption that claims submitted with an application are adequately described by the application. Claim 37 was present in substantially the same as claim 30 in the application as originally filed. It has simply been limited to food allergens as described on page 8 of the original specification. Claim 38-42 recites the properties on page 4, lines 8-14 and 26-28. Claim 44 recites the limitations found on page 12 and Example 3 (page 27). Claims 45-46 recite relevant subsets of food allergens that were described on pages 7-9 and the Examples of the specification as filed. Claims 56-61 recite the limitations found in original claim 30 and the data of Table 6 of the specification as filed.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The instant claims encompass *all* nucleotide molecule encoding *any* modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen such as the ones recited in claims 45 and 46. The specification discloses only three modified food allergens from peanut Ara h1, Ara h2 and Ara h3, much less about the polynucleotide encoding any modified food allergen.

In contrast to appellant's assertion that page 8 of the original specification describes nucleotide encoding modified food allergen, the specification on page 8 discloses latex allergen

from the rubber tree, *Hevea brasiliensis*, acidic proteins in the 8-14 kd and 22-24 kd range, much less about the *nucleotide molecule* encoding the modified food allergen.

In contrast to appellant's assertion that claim 44 recites the limitations found on page 12 and Example 3 (page 27), claim 44 recites the nucleotide of molecule encoding a modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen in a vector for expression in a host cell. The Example 3 on page 27 of the specification discloses modified peanut Ara h2 protein allergen where the amino acids at position 20, 31, 60 and 67 of the Ara h2 protein were changed to alanine by mutagenizing the gene encoding the protein and the protein was produced recombinantly. The cited passages do not disclose the nucleotide of molecule encoding a modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen in a vector for expression in a host cell.

In contrast to appellant's assertion that Claims 45-46 recite relevant subsets of food allergens that were described on pages 7-9 and the Examples of the specification as filed, claim 45 recites the nucleotide molecule encoding a modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen wherein the modified food allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks. Claim 46 recites the nucleotide mentioned above wherein the modified food allergen is based on a protein obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel

nut, soybean and shrimp. The specification on page 7-9 merely alludes to protein of the food allergens from peanuts, milk, grains such as Barley, soybeans, eggs, fish, crustaceans, and mollusks, codfish, hazel nut, and fish. The mere allusion to the protein food allergens mentioned above does not provide sufficient structure such as the nucleotide sequence encoding the modified food allergen wherein at least one amino acid has been modified in at least one or all IgE epitopes so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen.

In contrast to appellant's assertion that limitations of claims 56-61 can be found in original claim 30 and the data of Table 6 (page 27) of the specification, claims 56-61 encompass *all* nucleotide molecule encoding *any* modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen wherein 1-6 (claim 56), 1-5 (claim 57), 1-4 (claim 58), 1-3 (claim 59), 1-2 (claim 60) or 1 (claim 61) amino acid residue has been modified in the at least one IgE epitope. The Table 6 on page 27 of the specification discloses only the specific amino acid modification in the specific amino acid residues in only IgE binding of peanut allergen Ara h3, much less about the *nucleotide molecule* encoding *all* modified food allergen.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively. The specification discloses vector and host cell comprising said nucleotide for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino

acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A (T247A), P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

With the exception of the three specific polynucleotide molecules encoding the specific modified peanut allergens Ara h1, Ara h2 and Ara h3 mentioned above, there is inadequate written description about the structure associated with function of *all* nucleotide molecule encoding *all* modified food allergen, all nucleotide molecule encoding all modified food allergen based on *any* protein obtained from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, and all nucleotide molecule encoding *any* modified food allergen based on any protein obtained from a source such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean, shrimp, much less about the nucleotides encoding all modified food allergen wherein 1-6, 1-5, 1-4, 1-3, 1-2 or 1 amino acid in at least one IgE epitope have been modified without the nucleotide sequence and/or the corresponding amino acid sequence. There is in adequate written description about the structure of all nucleotide molecule encoding any modified food allergen because of the following reasons: A nucleotide molecule without the nucleotide sequence, the corresponding SEQ ID NO has no structure. There are inadequate written description about which nucleotides, codon, and the corresponding amino acids in at least one IgE epitope of which protein in which food allergen to be modified or substituted, for which amino acid, in turn, the corresponding nucleotide molecule encoding the undisclosed modified food allergen has reduced IgE binding and activates T cell as compared to any unmodified food allergen for making any modified food allergen. The specification does not provide a description of structural features that are common to IgE epitopes other than the peanut allergens specifically exemplified. The

specification does not provide a description of polynucleotide encoding all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from only three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make into nucleotides encoding other modified food allergen is adequately to described the genus defined by claim 37. In fact, the specification on page 4 at lines 10-11 discloses that IgE epitopes shared no common amino acid sequence motif. Even if the polynucleotide molecule is limited to peanut allergen, there is insufficient written description about the structure because "polynucleotide molecule" without SEQ ID NO has no structure, much less which amino acid in which IgE epitope of which protein is modified so that the modified food allergen has reduced IgE binding and activates T cells.

Furthermore, Appellant has not disclosed sufficient species of nucleotide encoding modified food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, and mollusks as encompassed by the claims. The specification discloses only polynucleotide molecules encoding only three peanut allergens Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of polynucleotide molecule encoding other modified food allergen from legumes other than peanut, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

At page 13-14 of the Brief, appellant argues whether written description requirement ever be satisfied for the claims relating to nucleotide molecules or protein without an explicit disclosure in the specification of every sequence encompassed by the claims. Appellant has already conceded that the Examiner is correct that the specification does not explicitly set forth the sequences of all possible disruption to Ara h1, Ara h2, and Ara h3 IgE sites. However, one skilled reading the specification, would understand, indeed would explicitly be told that the presented substitutions were merely exemplary and others would work as well.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The instant claims encompass *all* nucleotide molecule encoding *any* modified food allergen whose amino acid sequence is substantially identical to that of an

unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen such as the ones recited in claims 45 and 46.

The specification discloses only three food allergens from peanut Ara h1, Ara h2 and Ara h3 and the specific modification to the peanut allergen Ara h1, Ara h2 and Ara h3 such that the IgE epitopes of said peanut allergens have reduced IgE binding. The specification does not provide a description of polynucleotide encoding all modified food allergen other than the peanut allergens specifically exemplified. Neither the specification's description of exemplary modified IgE epitopes from three peanut allergens nor its general description of how those skilled in the art could find other IgE epitopes to make into nucleotides encoding other modified food allergen is adequately to described the genus defined by claim 37. In fact, the specification on page 4 at lines 10-11 discloses that IgE epitopes shared no common amino acid sequence motif. Until the critical nucleotides or codon, the corresponding amino acid residue(s) within the at least one IgE epitope essential for IgE antibody binding within the full length polypeptide in all food allergen have been identified and the corresponding amino acids to be substituted in said at least one IgE epitope has been described; in essence, the specification simply directs those skilled in the art to go figure out themselves what the claimed polynucleotide molecules look like. Thus, the specification's disclosure is inadequate to describe the claimed genus of nucleotide molecule encoding modified food allergen.

At page 15-16 of the Brief, Appellant submits that the specification explicitly sets out the sequence of several examples of nucleotide molecules that encode modified peanut allergens. The modified peanut allergens are described as "exemplary" of the inventive principles. For example, the specification recites that "Peanut allergens (Ara h1, Ara h2 and Ara h3) have been used in the examples to demonstrate alteration of IgE binding sites while retaining binding to IgG and activation of T cells" (page 4, lines 15-17). The specification also points to several other common food allergens (page 8, liens 1-3: examples of common food allergens include proteins from peanuts, milk, grains, such as wheat, and barley, soybeans, eggs, fish, crustaceans, and mollusks. The specification provides references for food allergens whose IgE epitopes have already been identified (page 8, liens 4-13). The specification describes techniques for

modifying sequences within the IgE sites (see for example, page 10, lines 3-6, and Examples 2-3) and for identifying those modifications that reduce IgE binding (See page 4, lines 24-28 and Examples 1-2) in accordance with claim 37. A person skill in the art would immediately understand the exciting implications of the inventive exemplification of reduced-allergenicity peanut allergens: if it works for peanuts, it will work for other food allergens. Appellant asserts that the present specification describes the invention of polynucleotide molecules encoded modified protein allergens for a wide variety of food allergens; the pending claims are of appropriate scope.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The instant claims encompass *all* nucleotide molecule encoding *any* modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen such as the ones recited in claims 45 and 46.

The specification discloses only polynucleotide encoding three food allergens from peanut Ara h1, Ara h2 and Ara h3 and the specific modification to the peanut allergen Ara h1, Ara h2 and Ara h3 such that the IgE epitopes of said peanut allergens have reduced IgE binding. The specification has not described the common feature of all IgE epitope of all protein in food allergens, much less about the nucleotide molecules encoding all modified food allergen. In fact, the specification on page 4 at lines 10-12 discloses that IgE binding epitopes shared no common amino acid sequence motif, let alone all nucleotide molecule encoding all modified food allergen as encompassed by claim 37. Further, the specification discloses substituting an alanine for arginine at position 152 of Ara h1 IgE epitope shown in SEQ ID NO: 2 resulted in increased IgE binding while substituting methionine at positions 144, 145, 147 and 148 of Ara h1 shown in SEQ ID NO: 2 resulted in decreased IgE binding (page 23, last paragraph, in particular).

In contrast to appellant's assertion that the specification the present specification describes the invention of polynucleotide molecules encoded modified protein allergens for a wide variety of food allergens, The specification on page 7-9 merely alludes to protein of the food allergens from peanuts, milk, grains such as Barley, soybeans, eggs, fish, crustaceans, and mollusks, codfish, hazel nut, and fish. The mere allusion to the protein food allergens mentioned

above does not provide sufficient structure such as the nucleotide sequence encoding the modified food allergen wherein at least one amino acid has been modified in at least one or all IgE epitopes so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen. Although the specification describes techniques for modifying sequences within the IgE sites (see for example, page 10, lines 3-6, and Examples 2-3) and for identifying those modifications that reduce IgE binding, the specification simply directs those skilled in the art to go figure out themselves what the claimed polynucleotide molecules look like without the polynucleotide or amino acid sequence of the modified food allergen.

Furthermore, Appellants has not disclosed sufficient species of nucleotide encoding modified food allergens from legumes other than peanut, milks, grains, eggs, fish, crustaceans, and mollusks as encompassed by the claims. Given the lack of a written description of *any* additional representative species of polynucleotide molecule encoding other modified food allergen from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, codfish, hazel nut soybean and shrimp, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, the specification's disclosure is inadequate to describe the claimed genus of nucleotide molecule encoding modified food allergen.

Claim Rejections - 35 USC § 112 New Matter

At page 17 of the Brief, Appellant submits that claim 37 does not include the language that the Examiner objects under this rejection. Thus claim 37 stands or falls alone and claims 59-60 stand or fall together. Appellant submits that claims 59-60 of a nucleotide molecule encoding a modified protein allergen that comprises at least one IgE epitope with 1-6, 1-5, 1-4, 1-3 or 1-2 modified amino acid residues. The original claim 30 recites "A nucleotide molecule encoding a modified allergen comprising at least one IgE binding site... modified by at least one amino acid change..." Appellant argues that original claim 30 makes it perfectly clear that the present invention encompasses nucleotide molecules encoding modified protein allergens with at least one IgE binding site that includes more than one modified amino acid residue. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively).

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. It is the Examiner's position that claim 37 should be included in this rejection because claims 59-60 dependent from claim 37. Pending claim 37 recites A nucleotide molecule encoding a modified *food allergen* whose amino acid sequence is substantially identical to that of an unmodified food allergen except that *at least* one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen. Pending claims 56-60 recite the nucleotide molecule encoding a modified food allergen mentioned above wherein 1-6, 1-5, 1-4, 1-3, 1-2 amino acid residues have been modified in the at least one IgE epitope. In contrast to appellant's argument that original claim 30 makes it perfectly clear that the present invention encompasses nucleotide molecules encoding modified protein allergens with at least one IgE binding site that includes more than one modified amino acid residue, the original claim 30 recites the nucleotide encodes modified protein allergen, and NOT modified food allergen. Further, the original claim 30 does not recite the specific species of "1-6", "1-5", "1-4", "1-3", and "1-2" amino acid residues have been modified in the at least one IgE epitope.

In response to appellant's argument that the specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (see epitopes 5, 7, 8, 9, 18 in Table 4 (page 25) and epitope 4 in Table 6 (page 27), it is noted that said specific epitopes in Table 4 on page 25 are limited to the IgE epitopes of modified peanut Ara h1, while the specific epitope 4 in Table 6 on page 27 is limited to the IgE epitope of modified peanut Ara h3. However, the rejected claims 37, and 56-60 are drawn to all nucleotide molecule encoding any modified *food allergen*, whose amino acid sequence is substantially identical to that of an unmodified food allergen except that *at least* one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen that include 1-6, 1-5, 1-4, 1-3, 1-2 in the at least one IgE epitope have been modified. Thus the original claim 30 and the specification do not have support for the polynucleotide molecule encoding all food allergen

wherein "1-6", "1-5", "1-4", "1-3", and "1-2" amino acid residues that have been modified in the at least one IgE epitope.

Claim Rejections - 35 USC § 103

Claims 37-45, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (of record, Eur. J. Biochem. 245: 334-339, April 1997; PTO 892) in view of Evens *et al* (of record, Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

At page 18 of the Brief, Appellant agues that Burks (1997) is not prior art. The relevant teachings of Burks (1997) were included near verbatim in USNN 08/717,933 filed September 23, 1996 (See pp. 135-155, 175, and 178-180) and USSN 09/141,220 filed August 27, 1998 (see page 7-11, and 16-29).

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The filing date of the instant claims 37-45, and 56-61 is deemed to be the filing date of instant application because (1) USSN 08/717,933 filed September 23, 1996 does not support the claimed limitations of A *nucleotide molecule* encoding any modified *food allergen* whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen of the instant application. (2) Further, the pages 135-155, 175, and 178-180 of USSN 08/717,933 that appellant referring to do not disclose the claimed limitation of polynucleotide encoding any modified food allergen as set forth in claim 37. (3) Similarly, the specification on page pp. 7-11, and 16-29 of USSN 09141,220 that appellant referring to does not disclose the claimed limitation of polynucleotide encoding any modified food allergen as set forth in claim 37. (4) Because the pending claims are NOT drawn to polynucleotide encoding modified peanut allergen, the pending Claims 37-45, and 56-61 can only have the benefit of the filing date of instant application. Thus Burks *et al* (Eur. J. Biochem. 245: 334-339, April 1997) is a prior art reference because the reference is published in April 1997.

Claims 37-46, and 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley *et al* (of record, Archives of Biochemistry and Biophysics 342(2): 244-253, June

1997; PTO 1449) in view of Evens *et al* (of record, Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

At paragraph bridging page 18-19 of the Brief, Appellant agues that Stanley (1997) is not prior art and the relevant teachings of Stanley were included near verbatim in USNN 08/717,933 filed September 23, 1996 (See pp. 135-155, 175, and 178-180) and USSN 09/141,220 filed August 27, 1998 (see page 7-11, and 16-29).

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The filing date of the instant claims 37-45, and 56-61 is deemed to be the filing date of instant application because (1) USSN 08/717,933 filed September 23, 1996 does not support the claimed limitations of A *nucleotide molecule* encoding any modified *food allergen* whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen of the instant application. (2) Further, the pages 135-155, 175, and 178-180 of USSN 08/717,933 that appellant referring to do not disclose the claimed limitation of polynucleotide encoding any modified food allergen as set forth in claim 37. (3) Similarly, the specification on page pp. 7-11, and 16-29 of USSN 09141,220 that appellant referring to does not disclose the claimed limitation of polynucleotide encoding any modified food allergen as set forth in claim 37. (4) Because the pending claims are NOT drawn to polynucleotide encoding modified peanut allergen, the pending Claims 37-46, and 56-61 can only have the benefit of the filing date of instant application. Thus Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997) is a prior art reference because the reference is published in April 1997.

Claim Rejections - obviousness-type double patenting

At page 19-20 of the Brief, Appellant submits that claims 1-4 of U.S. Pat. No. 6,486,311 are drawn to a nucleotide molecule that encodes Ara h2. Claim 7 is a nucleotide molecule that encodes an Ara h2 with one or more mutated IgE epitopes. In contrast, the present claims are to a nucleotide molecule that encodes a modified food allergen. The present claims are of different scope, and are not obvious over one another. Appellant submits that Ara h2 are non-obvious over the pending food claims because they represent a non-obvious species of the claimed genus. As

discussed in the specification, peanut allergens such as Ara h2 are one of the most potent of allergens (page 16, lines 4-11). Based solely on the present modified allergen claims, a skilled person would have lack a reasonable expectation of success that is necessary to render obvious the modified Ara h2 species claims. Appellant submits that a skilled person would recognize that a generic claim to a modified food allergens cannot render obvious a claim that is limited to modified Ara h2.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons. The polynucleotide encoding the modified peanut allergen Ara h2 (species) in claim 7 of '311 patent anticipates the polynucleotide encoding the modified food allergen (genus) of the pending claims 37-46 and 56-61 of instant application because species anticipates a genus. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Further, the method of making the modified peanut allergen such as Ara h1 as evidence in the instant specification on page 25, (Table 4, amino acids critical to IgE binding of Ara h1) is the same as that of Table 6, col. 18 of the '331 patent. Likewise, the method of making the modified food allergen such as Ara h2 as evidence in the instant specification on page 26, Table 5 is the same as that of Table 10, col. 28 of '311 patent.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Phuong N. Huynh, Ph.D.
September 30, 2004

Conferees
Christina Chan
SPE, Art unit 1644

James Housel
SPE, Art unit 1648